within at least one complementarity determining region to partially or fully replace said complementarity determining region.

24. (Amended) The composition of claim **[67]** 66 wherein said protein fragment or peptide comprising a T cell receptor antagonist **[derived from proteolipid protein]** comprises a peptide analog of **[proteolipid protein]** a peptide which induces a T cell response.

29. (Amended) The composition of claim 27 wherein said composition comprises a fusion protein in which said protein fragment or peptide comprising a T cell receptor antagonist **[derived from proteolipid protein]** is covalently joined to said immunoglobulin or portion thereof.

66. (Amended) A composition comprising an immunoglobulin or a portion thereof linked to a protein fragment or peptide, wherein said immunoglobulin or portion thereof is capable of binding to an Fc receptor and said protein fragment or peptide comprises a T cell receptor antagonist **[derived from proteolipid protein]**, said composition having the property of being endocytosed by cells bearing said Fc receptor and processed by the cells to present said T cell receptor antagonist in association with endogenous MHC Class II molecules, thereby inactivating T cells for an extended period of time.

68. (Amended) The composition of Claim 66, wherein said protein fragment or peptide comprising a T cell receptor antagonist **[derived from proteolipid protein]** is covalently linked to said immunoglobulin or portion thereof.

69. (Amended) The composition of Claim 68, wherein said protein fragment or peptide comprising a T cell receptor antagonist **[derived from proteolipid protein]** comprises a peptide analog of proteolipid protein.

72. (Amended) The composition of Claim 67, wehrein the composition comprises a fusion protein in which said protein fragment or peptide comprising a T cell receptor antagonist [**derived from proteolipid protein**] is covalently joined to said immunoglobulin or portion thereof.

73. (Amended) The composition of Claim 72, wherein said protein fragment or peptide comprising a T cell receptor antagonist [**derived from proteolipid protein**] is positioned within at least one complementary determining region to partially or fully replace said complementarity determining region.

Please add the following new claims:

74. The composition of Claim 66, wherein said T cell receptor antagonist is derived from proteolipid protein.

75. The composition of Claim 66, wherein said T cell receptor antagonist is derived from myelin basic protein.

I. Interview of September 21, 2000

Applicant thanks the Examiner for extending the courtesy of a telephonic interview on September 21, 2000 during which the rejections asserted in the Final Office Action of April 13, 2000 were discussed. During the interview, the Examiner acknowledged that there was no suggestion in the Bona and Kuchroo references that the claimed compositions would be effective in inactivating T cells for an extended period of time, as discussed in the comments below and the accompanying Declaration of Habib Zaghouani.

During the interview, the Examiner also indicated that the claims could be extended to cover T cell antagonists derived from molecules other than proteolipid protein upon Applicant's provision of data showing the effectiveness of such compositions. As suggested by the Examiner, the accompanying Declaration of Habib Zaghouani provides data showing that immunoglobulins comprising T cell antagonists derived from myelin basic protein were also effective in treating autoimmune disease.

Applicants note that the specification describes the prevention of T cell activation throughout. For example, the prevention of T cell activation is described at page 16, line 29 through page 17, line 1. Applicant further notes that inactivation of T cells for an extended period is an inherent property of the claimed compositions which may be included in the claims. (See *Kennecott Corporation v. Kyocera International, Inc.*, 5 U.S.P.Q. 2d 1194 (Fed. Cir. 1987).

II. Sequence Listing

As requested by the Examiner, paper and computer readable copies of a Sequence Listing containing the sequences described in the specification are provided herewith.

III. Rejection of Claims 4, 6, 9, 11, 24, 26, 27, 29, 66-70, and 72-73 Under 35 U.S.C. §103

Claims 4, 6, 9, 11, 24, 26, 27, 29, 66-70, and 72-73 were rejected under 35 U.S.C. §103 on the assertion that they are obvious over Bona et al. in view of Kuchroo et al. The Examiner asserts that the data provided in the Declaration submitted March 22, 2000 was insufficient to demonstrate that the claimed compositions permanently eliminated disease in mice. The Examiner also asserts that the results obtained with the claimed compositions are not unexpected, since they are consistent with the increased half life of peptides embedded in immunoglobulin backbones relative to free peptides.

As acknowledged by the Examiner during the telephonic interviews of September 21, 2000, Applicant submits that, as discussed in the accompanying Declaration, the claimed compositions permanently eliminated disease symptoms in mice. The data included in Exhibit B of the Declaration submitted March 22, 2000 demonstrates that 2 month old mice treated with the claimed compositions did not develop disease symptoms for a period of 120 days from administration (i.e. the mice did not develop disease as of approximately 6 months of age). As indicated in the accompanying Declaration, mice have very poor susceptibility to EAE once they reach the age of 24-27 weeks (6 months). Thus, the claimed compositions permanently eliminated disease symptoms.

Furthermore, as discussed in the interview of September 21, 2000 and indicated in the accompanying Declaration, the permanent elimination of disease symptoms is not a consequence of increased half life. The results shown in Exhibit B of the Declaration submitted March 22, 2000 demonstrated that mice treated with the claimed compositions did not develop disease for a period of 15 weeks from administration of the claimed compositions. As indicated in the accompanying Declaration, the half life of immunoglobulins is on the order of 4.5 days. Thus, by 15 weeks from administration, the amount of immunoglobulin remaining in the treated subjects is negligible. As indicated in the accompanying Declaration, it is unlikely that a sufficient amount of the immunoglobulin remains after such an extended time period to provide direct protection from disease. Rather, the observed protection reflects a permanent inactivation of the T cells directed against the antigen responsible for the autoimmune disease.

In addition, Applicant notes that, as discussed during the interview of September 21, 2000 and indicated in the accompanying Declaration, the claimed compositions inactivate T cells by binding to newly synthesized MHC molecules after being internalized into the antigen presenting cell. There is no suggestion of this mechanism in Bona, since the actual working examples disclosed in Bona relate to compositions intended to activate an immune response against an antigen embedded in an immunoglobulin rather than to suppress an immune response by inactivating T cells. Furthermore, as discussed in paragraph 6 of the accompanying Declaration, the speculation in the Bona reference relating to inserting self-antigens (as opposed to the T cell receptor antagonists used in the claimed compositions) into immunoglobulins indicates that Bona hypothesized that the self antigens would work by preventing pathogenic peptides from binding to MHC proteins so the pathogenic T cells will not be activated. However, under the mechanism hypothesized by Bona, these pathogenic T cells remain potentially harmful as they were not inactivated.

As discussed during the interview of September 21, 2000 and in the accompanying Declaration, the compositions of Kuchroo cannot operate via the intracellular mechanism utilized by the claimed compositions, since the compositions of Kuchroo are free peptides which cannot be internalized and would have to displace other peptides to bind to the MHC proteins on the surface of the antigen presenting cells. As discussed in the accompanying Declaration, this approach would not be effective because of the unlimited supply of self antigen provided by the host.

In addition, as indicated in the accompanying Declaration and in Exhibit E provided therewith, immunoglobulins containing a T cell receptor antagonist derived from a protein other than proteolipid protein were also effective in suppressing autoimmune disease. Thus, compositions comprising an immunoglobulin or portion thereof containing a T cell receptor antagonist are generally effective in treating disease.

In view of the above, Applicant respectfully requests that the rejection under 35 U.S.C. §103 be withdrawn.

III. Conclusion

During the interview of September 21, 2000 the Examiner acknowledged that there was no suggestion in Bona or Kuchroo that the claimed compositions would be effective in inactivating T cells over an extended period of time. The Examiner also suggested that Applicants could obtain claims which were not limited to immunoglobulins or portions thereof comprising T cell receptor antagonists derived from proteolipid protein upon providing additional data showing that immunoglobulins or portions thereof comprising T cell receptor antagonists derived from other proteins were also effective. Applicants have provided the requested data in the accompanying Declaration.

In view of the foregoing, it is submitted that the claims are in condition for allowance. Reconsideration and withdrawal of the rejections is respectfully requested. Should the Examiner have any questions regarding this matter he is invited to telephone the undersigned so that the questions may be resolved.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410. A duplicate copy of this sheet is enclosed.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: _____

By: _____

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